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Exercise for vasomotor menopausal symptoms (Review)

Daley A, Stokes-Lampard H, Thomas A, MacArthur C

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[Intervention Review]

Exercise for vasomotor menopausal symptoms

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ABSTRACT

Background

Evidence suggests that many perimenopausal and early postmenopausal women will experience menopausal symptoms; hot flushes are the most common. Symptoms caused by fluctuating levels of oestrogen may be alleviated by hormone therapy (HT), but a marked global decline in its use has resulted from concerns about the risks and benefits of HT. Consequently, many women are seeking alternatives. As large numbers of women are choosing not to take HT, it is increasingly important to identify evidence-based lifestyle modifications that have the potential to reduce vasomotor menopausal symptoms.

Objectives

To examine the effectiveness of any type of exercise intervention in the management of vasomotor symptoms in symptomatic perimenopausal and postmenopausal women.

Search methods

Searches of the following electronic bibliographic databases were performed to identify randomised controlled trials (RCTs): Cochrane Menstrual Disorders and Subfertility Group Specialised Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley Internet interface), MEDLINE (Ovid), EMBASE (Ovid), PsycINFO (Ovid), the Science Citation Index and the Social Science Citation Index (Web of Science), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (Ovid) and SPORTDiscus. Searches include findings up to 3 March 2014.

Selection criteria

RCTs in which any type of exercise intervention was compared with no treatment/control or other treatments in the management of menopausal vasomotor symptoms in symptomatic perimenopausal/postmenopausal women.

Data collection and analysis

Five studies were deemed eligible for inclusion. Two review authors independently selected the studies, and three review authors independently extracted the data. The primary review outcome was vasomotor symptoms, defined as hot flushes and/or night sweats. We combined data to calculate standardised mean differences (SMDs) with 95% confidence intervals (CIs). Statistical heterogeneity was assessed using the I^2 statistic. We assessed the overall quality of the evidence for main comparisons using GRADE (Grades of Recommendation, Assessment, Development and Evaluation) methods.

Main results

We included five RCTs (733 women) comparing exercise with no active treatment, exercise with yoga and exercise with HT. The evidence was of low quality: Limitations in study design were noted, along with inconsistency and imprecision. In the comparison of exercise versus no active treatment (three studies, n = 454 women), no evidence was found of a difference between groups in frequency or intensity of vasomotor symptoms (SMD -0.10, 95% CI -0.33 to 0.13, three RCTs, 454 women, I^2 = 30%, low-quality evidence). Nor was any evidence found of a difference between groups in the frequency or intensity of vasomotor symptoms when exercise was compared with yoga (SMD -0.03, 95% CI -0.45 to 0.38, two studies, n = 279 women, I^2 = 61%, low-quality evidence). It was not possible to include one of the trials in the meta-analyses; this trial compared three groups: exercise plus soy milk, soy milk only and control; results favoured exercise relative to the comparators, but study numbers were small. One trial compared exercise with HT, and the HT group reported significantly fewer flushes in 24 hours than the exercise group (mean difference 5.8, 95% CI 3.17 to 8.43, 14 participants). None of the trials found evidence of a difference between groups with respect to adverse effects, but data were very scanty.

Authors' conclusions

Evidence was insufficient to show whether exercise is an effective treatment for vasomotor menopausal symptoms. One small study suggested that HT is more effective than exercise. Evidence was insufficient to show the relative effectiveness of exercise when compared with HT or yoga.

PLAIN LANGUAGE SUMMARY

Exercise for vasomotor menopausal symptoms

Review question: Is exercise an effective treatment for reducing hot flushes/night sweats in menopausal women with hot flushes?

Background: Studies suggest that a high proportion of menopausal women will experience hot flushes and night sweats. Hormone therapy is considered to be the most effective treatment for symptoms. However, studies have reported that hormone therapies are potentially associated with some negative health effects; many women are now choosing not to use these and are looking for alternatives. Therefore, it is increasingly important to identify lifestyle modifications that may help to reduce the frequency and severity of hot flushes and night sweats. Review authors from The Cochrane Collaboration examined the evidence, which is current to March 2014.

Study characteristics: Five studies randomly assigned 762 women experiencing hot flushes/night sweats. Three trials and two trials, respectively, were included in pooled comparisons of exercise versus control (n = 454 women) and exercise versus yoga (n = 279 women). One small study (14 women) compared exercise versus hormone therapy.

Key findings: When exercise was compared with no intervention, no evidence was found of any difference in their effect on hot flushes. One small study suggested that HT is more effective than exercise. Evidence was insufficient to show whether exercise was more effective than yoga. None of the trials found any evidence of differences between groups with respect to adverse effects, but data were very scanty.

Quality of the evidence: The methodological quality of the studies was variable. We assessed the evidence as of low quality: The main limitations were poor reporting of study methods, inconsistent results and lack of precision.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Exercise versus control for vasomotor menopausal symptoms

Population: women with vasomotor menopausal symptoms
Setting: university
Intervention: exercise versus no active treatment

Outcomes	Illustrative comparative risks* (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Exercise versus no active treatment			
Change in hot flushes/night sweats Self-report[1] Follow-up: 3 to 24 months	Mean change in hot flushes/night sweats is **0.10 standard deviations lower in the exercise groups** (-0.33 lower to 0.13 higher)	454 (3 studies)	⊕◯◯◯ **Low**[a,b,c]	SMD -0.10 (-0.33 to 0.13)

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a] Evidence self-reported: validated scales or logs/diaries used.
[b] Recruitment, method of determining menopausal status and characteristics of included women varied.
[c] Variation in the direction of effect.

BACKGROUND

Description of the condition

Menopause is a significant event in most women's lives, as it marks the end of natural reproductive life. The perimenopausal and early postmenopausal period is typically characterised by fluctuating levels of endogenous oestrogen, which can give rise to symptoms that are severe and disruptive. Evidence suggests that a high proportion of perimenopausal and early postmenopausal women will experience some menopausal symptoms; hot flushes are common (Greendale 1999). Large cultural differences are apparent in the experience of vasomotor symptoms; women living in Western industrialised countries are more likely to experience these than other populations of women (Gold 2004; Reed 2013). Hot flushes (called hot flashes in USA) occur as a sudden feeling of heat in the face, neck and chest (WHO 1996). Hot flushes are frequently accompanied by skin flushing and perspiration; a chill may follow

as core body temperature drops (Greendale 1999). Hot flushes can be occasional or frequent, can last a few seconds to an hour, may be spontaneous and unpredictable and can vary in severity (Freeman 1995). Hot flushes that occur during the night are typically referred to as night sweats. Flushes and night sweats are of concern in themselves, but they also can disrupt sleep patterns and alter daily activities, which can lead to fatigue and decreased quality of life (NAMS 2002). Hot flushes are thought to result from the brain's response to diminished hormones and hormonal fluctuations that occur during the menopause transition, which in turn leads to instability of thermoregulatory mechanisms that regulate temperature homeostasis in the hypothalamus (Freeman 2001).

Hormone therapy (HT) (oestrogen or combined oestrogen-progestogen therapy) is the most common treatment for hot flushes; the North American Menopause Society (NAMS 2012) supports its use in treating moderate to severe vasomotor symptoms. However, apparent benefits of HT have been questioned in the past decade because trials (Hulley 1998; Viscoli 2001; WHI 2002) failed to demonstrate that HT is associated with secondary prevention of cardiovascular disease. These publications raised concerns about the risks and benefits of HT. Several other trials and observational studies (Holmberg 2004; Million Women Study 2003; Rossouw 2002) have reported that HT may be linked with increased risk of certain diseases, including breast cancer. Whilst the reanalysis (Rossouw 2007) of the Women's Health Initiative in 2007 provided evidence of coronary heart safety for users of HT younger than 60 years of age and within 10 years of the onset of menopause, previous uncertainty surrounding actual cost/benefit to be gained has left many women reluctant to take HT. Doctors are more cautious about prescribing HT, as demonstrated by the large reduction in prescriptions in recent years (Hersh 2004; Lawton 2003). In addition, evidence (Hope 1998) has suggested that some women report adverse effects when taking HT, which may preclude hormone use, and not all women are able to use HT. Consequently, many women are seeking alternatives (Daley 2006; Nelson 2005; Posadzki 2013), and it has become increasingly important to identify other evidence-based interventions that have the potential to reduce vasomotor and other menopausal symptoms.

Description of the intervention

Numerous studies and reviews (Daley 2008; DH 2011; Eriksen 2004) involving other populations have reported that physical activity and exercise participation may have positive effects on a range of other menopause-related symptoms and health outcomes such as cognitive functioning, depression, sleep patterns, fatigue, bone density, weight maintenance and cardiovascular disease. Thus, it is reasonable to investigate whether exercise will have an impact on menopausal vasomotor symptoms. In addition to providing significant physiological benefits (e.g. cardiovascular and bone health), exercise may represent one of the promising alternatives to HT and, if it is demonstrated to be effective in the treatment of vasomotor symptoms, offers an inexpensive intervention that typically has few known side effects. The Royal College of Obstetricians and Gynaecologists (RCOG 2006) in the United Kingdom (UK) has advised (Scientific Advisory Committee Opinion Paper 6) that women who are more active tend to suffer less from the symptoms of menopause, and that the best type of activity is aerobic, sustained, regular exercise such as swimming and running.

Observational studies have reported inconsistent findings regarding the association between exercise and lower rates of vasomotor symptoms, although larger studies have tended to report positive associations, and smaller studies negative or no associations. Among women attending menopause clinics in Italy (n = 66,501), severe vasomotor symptoms were significantly more common in those reporting lower levels of regular physical activity (Progetto Study 2005). A similar association was found in a study of a multiracial population of women (N = 12,245) (Gold 2000). A low vasomotor symptom score was found to be correlated with regular exercise and regular free-time activities (n = 4504) (Stadberg 2000). A recent longitudinal study (13-year follow-up) has reported that exercise participation was associated with shorter symptom duration (Col 2009), but the sample was small (n = 205). Other smaller observational studies (typically n < 1500) have reported negative or no associations (Daley 2007a; Sternfeld 1999; Wilbur 1992), but these smaller studies generally have not considered relevant confounding variables.

Although large observational studies have indicated that exercise might be a useful intervention in helping to ameliorate vasomotor symptoms, these findings must be substantiated in randomised controlled trials (RCTs). In 2011 the Cochrane review titles "Exercise for the Management of Vasomotor Menopausal Symptoms" included six studies that were generally small. Thus, no conclusions regarding the effectiveness of exercise as a treatment for vasomotor symptoms could be made by review authors at that time.

How the intervention might work

Plausible biological mechanisms are known by which exercise could reduce vasomotor and other menopausal symptoms. It has been hypothesised that endorphin concentrations in the hypothalamus decrease as oestrogen production declines, enhancing the release of norepinephrine and serotonin. Exercise may have a similar effect to HT in the amelioration of vasomotor symptoms by increasing hypothalamic and peripheral β-endorphin production (Bortz 1981). In addition, evidence suggests that as endorphins increase, the frequency and amplitude of luteinising hormone decrease, and this regulates gonadotropin-releasing hormone levels (Reid 1981). Research (Heitkamp 1996) has shown that active individuals have higher basal levels of β-endorphins than those who are inactive. Through these mechanisms, exercise may help to stabilise the thermoregulatory centre and diminish the risk of

hot flushes. It has also been suggested that exercise can improve mental health outcomes by providing a distraction or 'time out' strategy from daily worries (Bahrke 1978), and that exercise can enhance feelings of accomplishment among individuals, thereby improving self-esteem (Fox 2000).

Why it is important to do this review

If shown to be effective, exercise might be an acceptable, low-cost, non-pharmacological treatment for vasomotor menopausal symptoms and an alternative to HT. Exercise may confer additional physical and mental health benefits (e.g. improve cardiovascular and bone health, decrease feelings of depression) for perimenopausal and early postmenopausal women.

OBJECTIVES

To examine the effectiveness of any type of exercise intervention in the management of vasomotor symptoms in symptomatic perimenopausal and postmenopausal women.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) were eligible for inclusion. Cross-over trials were eligible for inclusion, but only data from the first phase were included in meta-analyses.

Types of participants

Studies of women with surgical or spontaneous menopause, in the perimenopausal or postmenopausal period, experiencing any vasomotor symptoms at baseline and recruited from any setting or population-based sample were eligible for inclusion.
Perimenopausal women were defined as women with spontaneous menopause who had experienced irregular menstruation within the previous 12 months. Postmenopausal women were defined as women with surgical or spontaneous menopause and amenorrhoea for longer than 12 months.
Women experiencing vasomotor symptoms due to breast cancer treatment and women taking any hormone therapy for any reason before the time of study entry were excluded.

Types of interventions

Exercise was defined as structured exercise and/or physical activity achieved through active living. Trials that compared any type of exercise intervention with no active treatment or with other treatments were included.
Active treatments used as controls could include hormone therapy (HT), dietary supplementation, health education and alternative forms of exercise (e.g. yoga, tai chi). When trials compared more than one form of exercise, the intervention was as defined by the study author.
In cases in which the study author did not define the intervention, the less aerobically vigorous form of exercise was deemed the control comparator.
Co-interventions could include instruction in lifestyle/health education or health and exercise awareness and complementary and alternative medicine.
Any dosage or duration of intervention was included.
No restriction was placed on who delivered the intervention (i.e. researchers, primary health practitioners, physical activity professionals, health promotion agencies and medical doctors).
Interventions not involving exercise were excluded.

Types of outcome measures

- Vasomotor symptoms assessed by any method. Vasomotor symptoms were defined as hot flushes and/or night sweats. If more than one assessment of vasomotor symptoms was included, preference was given to the primary outcome if this was specified. If this was not specified, validated assessments were preferred over unvalidated assessments.
- Individual symptoms, for example, severity or frequency, or both, of hot flushes and night sweats.

Primary outcomes

- Effectiveness: frequency or intensity of vasomotor menopausal symptoms.

Secondary outcomes

- Any adverse effects of exercise interventions.

Search methods for identification of studies

We searched for all published and unpublished RCTs of exercise for vasomotor menopausal symptoms, without language restriction and in consultation with the Menstrual Disorders and Subfertility Group (MDSG) Trials Search Co-ordinator.
Searches for this review were first conducted in 2006 (between 1 and 2 June 2006). Searches for the first update of this review were conducted between 17 and 22 June 2009, and again between 16

and 24 March 2010. For this second update, searches were conducted on 3 March 2014. Searches were based on text words and index terms, when available, encompassing vasomotor symptoms, hot flushes, hot flashes, night sweats, nocturnal sweats, exercise, physical activity, physical training, yoga, tai chi, walking, running, jogging, swimming and cycling.

Electronic searches

Searches of the following electronic bibliographic databases were performed to identify RCTs: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and PsycINFO. Science Citation Index and Social Science Citation Index, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and SPORTDiscus databases were searched for previous versions of this review, but not in this update.

The Cochrane Menstrual Disorders and Subfertility Group Specialised Trials Register was not searched in the first version of this review but was searched in both updates (16 March 2010 and 3 March 2014) and will be included in future updates. The search string for this register can be found in Appendix 1.

Search strategies can be found in Appendix 2.

Information about ongoing trials and recently completed research studies was obtained by searching Current Controlled Trials, ClinicalTrials.gov and UK Clinical Research Network Portfolio Database. A series of searches (3 March 2014) were performed using the following terms: flush, flushes, flash, flashes, sweats, sweating, nocturnal sweats, menopause.

Searching other resources

Handsearches of relevant journals and published conference abstracts were performed. The following journals were handsearched: *Medicine and Science in Sport and Exercise*, *Maturitas*, *Menopause*, *Health Psychology*, *Journal of Women's Health*, *Women and Health*, *Obstetrics and Gynecology*, *Sports Medicine*, *British Journal of Obstetrics and Gynaecology* and *American Journal of Obstetrics and Gynecology*.

Citation lists of relevant publications, review articles and included studies were also searched.

Data collection and analysis

Data collection and analysis were conducted in accordance with recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Selection of studies

Marian Showell (Trials Search Co-ordinator for the Cochrane Menstrual Disorders and Subfertility Group) and review authors conducted the electronic searches for this 2014 update. Two review authors (AD, AT) independently selected reports potentially fulfilling the inclusion criteria of this review on the basis of title and abstract. Full articles of any possibly relevant reports were retrieved for more detailed evaluation. Both review authors then independently performed a final selection of trials to be included in the review by using a standardised form (eligibility form plus instruction sheet for assessing eligibility that was designed for this review). Reports were excluded according to the first criterion that they failed to fulfil. Disagreements were resolved by consensus. The principal author of the study was contacted by a review author (AD) when additional information about the trial was needed for a decision regarding the eligibility of reports.

Data extraction and management

For this 2014 update, data were independently extracted by two review authors (AD, AT) using a data extraction form designed by the review authors. When disagreements could not be resolved by consensus, a third review author (HSL) was consulted to resolve discrepancies. Additional information on trial methodology, participants and study results was sought from the first or corresponding author of some studies that appeared to meet the eligibility criteria. This occurred when aspects of methodology were unclear, when data were provided in a form unsuitable for meta-analysis or when the vasomotor symptom status of participants was unclear. When studies were followed by multiple publications, the main trial report was used as the reference and was supplemented by additional details from secondary papers.

Assessment of risk of bias in included studies

The included studies were assessed for risk of bias using the Cochrane risk of bias assessment tool to assess sequence generation; allocation concealment; blinding of participants, providers and outcome assessors; completeness of outcome data; selective outcome reporting; and other potential sources of bias. All review authors independently assessed these six domains, with disagreements resolved by consensus discussion. Results are presented in risk of bias tables for each included study.

Measures of treatment effect

For continuous data, mean differences between treatment groups were calculated if all studies reported exactly the same outcomes. If similar outcomes were reported on different scales, the standardised mean difference was used. Ordinal data were treated as continuous data.

A random-effects approach was used to calculate summary effect measures, as a priori it was expected that analyses would have heterogeneous results.

For dichotomous data, the numbers of events in the control and intervention groups of each study were used to calculate Peto odds ratios.
Confidence intervals (95%) were presented for all outcomes and comparisons.

Unit of analysis issues

We planned to include all cluster-randomised trials in the analyses, along with individually randomised trials. We adjusted sample sizes or standard errors using the methods set out in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If both cluster-randomised trials and individually randomised trials were included, we planned to synthesise relevant information. We considered it reasonable to combine the results from both when little heterogeneity was noted between study designs, and when interaction between effects of the intervention and choice of the randomisation unit was considered unlikely.
In cross-over trials, we planned to include only data from the first phase in the meta-analysis.

Dealing with missing data

As far as possible, data were reported using an intention-to-treat analysis, and attempts were made to obtain missing data from the original investigators.

Assessment of heterogeneity

Heterogeneity was considered by the review authors when clinical and methodological characteristics of included studies were similar enough for a meta-analysis to yield a meaningful summary. Statistical analyses were performed in accordance with the guidelines for statistical analysis developed by The Cochrane Collaboration (Higgins 2011). Heterogeneity between the results of different studies was assessed by the I^2 statistic (a quantity that describes approximately the proportion of variation in point estimates that is due to heterogeneity rather than sampling error), which can be interpreted in these broad terms.

- 0% to 40%: might not be important.
- 30% to 60%: represents moderate heterogeneity.
- 50% to 90%: represents substantial heterogeneity.
- 75% to 100%: represents considerable heterogeneity

(Higgins 2011).

Assessment of reporting biases

The review authors aimed to minimise the potential impact of reporting bias by ensuring a comprehensive search for eligible studies and by staying alert for duplication of data. It was planned that a funnel plot would be prepared if 10 or more studies were identified. However, too few studies were identified for construction of a funnel plot.

Data synthesis

When possible, data from included studies were combined using random-effects models in the following comparisons.

- Exercise versus inactive control.
- Exercise versus yoga.
- Exercise versus HT.

Subgroup analysis and investigation of heterogeneity

Data permitting, subgroup analyses were performed to determine separate evidence for the following.

- Perimenopausal women.
- Postmenopausal women.
- Different co-interventions.
- Intervention duration (up to 6 months vs 6 months or longer).

Sensitivity analysis

We conducted a sensitivity analysis for the primary outcomes to determine whether review conclusions would have differed if eligibility were restricted to studies at low risk of bias (i.e. studies not deemed at high risk of bias in any domain and reporting acceptable methods of randomisation and allocation concealment).

Overall quality of the body of evidence: 'Summary of findings' table

We prepared a 'Summary of findings' table using Guideline Development Tool software. This table evaluated the overall quality of the body of evidence for the primary review outcome using GRADE (Grades of Recommendation, Assessment, Development and Evaluation) criteria (study limitations (i.e. risk of bias), consistency of effect, imprecision, indirectness and publication bias).

RESULTS

Description of studies

Results of the search

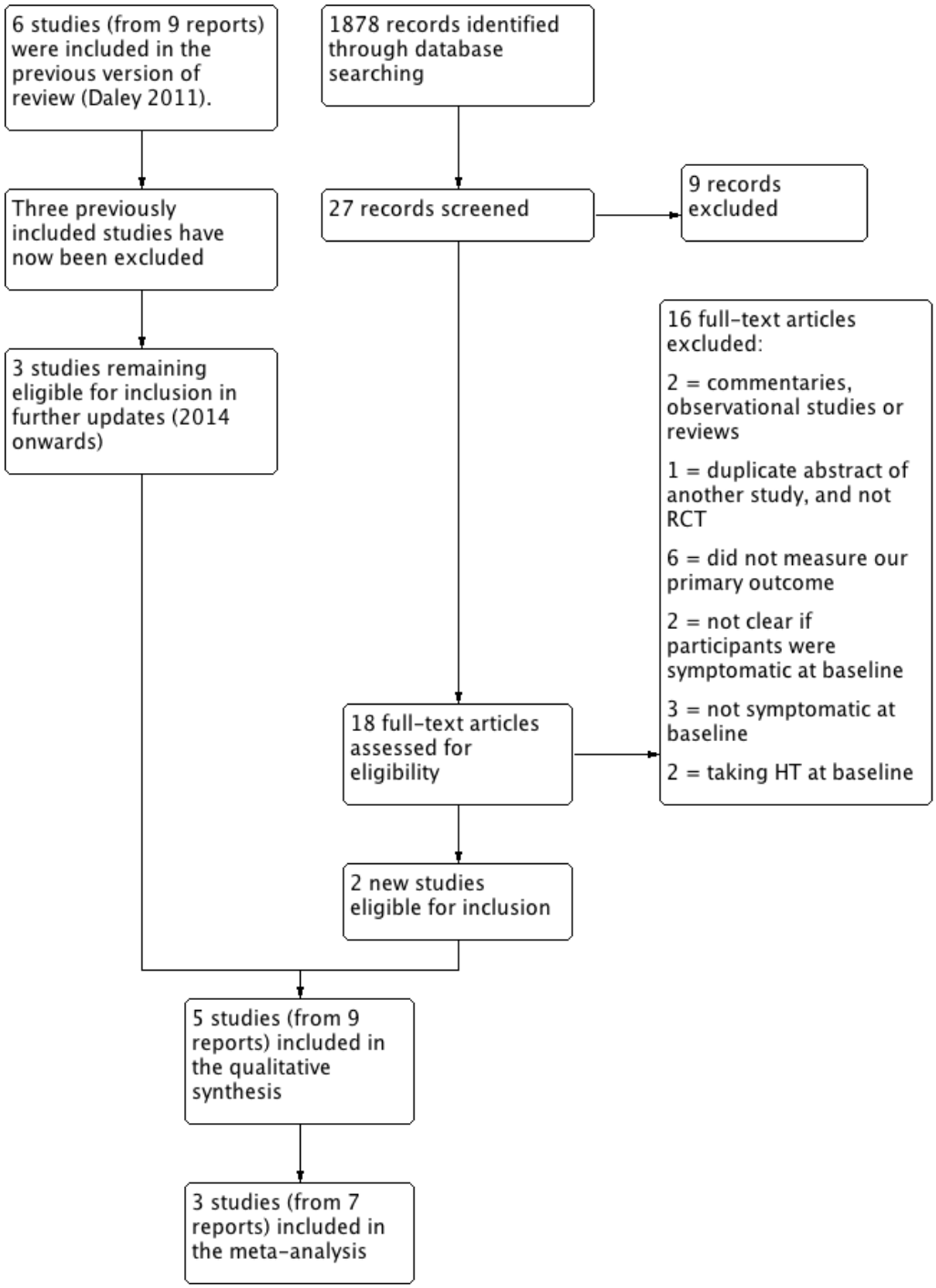
In the 2007 version of this review, through a comprehensive literature search, 655 potentially relevant references were identified and screened for retrieval. A total of 603 references were excluded on the basis of title and abstract, and 52 references were retrieved for more detailed evaluation. Of these, and after further scrutiny, 33 publications were not considered suitable for inclusion in the review, as they were commentaries, observational studies or reviews,

and 18 publications initially considered eligible on the basis of information contained in the abstract were subsequently excluded after the full study report had been evaluated (see below). Thus, one study (Lindh-Åstrand 2004) was eligible for inclusion in the 2007 version of this review (see Included studies section below).

For the first update of the review (2011), a further 557 potentially relevant references were identified and screened for retrieval. A total of 513 references were excluded on the basis of title and abstract, and 44 references were retrieved for more detailed evaluation. Of these, and after further scrutiny, 24 publications were not considered suitable for inclusion in the review, as they were commentaries, observational studies or reviews, and 12 publications initially considered eligible on the basis of information contained in the abstract were subsequently excluded after the full study report had been evaluated (see below). Thus an additional eight reports (five studies: Bergström 2005; Chatta 2008; Elavsky 2007; Hanachi 2008; Moriyama 2008) were identified as eligible, meaning that a grand total of six studies (nine reports) were eligible for inclusion.

For this second update of the review (2014), a further 1878 potentially relevant references were identified by the searches, and 27 were screened for retrieval. A total of nine references were excluded on the basis of title and abstract, and 18 references were retrieved for more detailed evaluation. Of these, and after further scrutiny, two publications were not considered suitable for inclusion in the review, as they were commentaries, observational studies or reviews, and 14 publications initially considered eligible on the basis of information contained in the abstract were subsequently excluded after the full study report had been evaluated (see below). Therefore two studies were eligible for inclusion (Luoto 2012; Sternfeld 2014). For details of study screening and selection, see Figure 1.

Figure 1. Study flow diagram.



Included studies

In this second update of the review (2014), on the advice of the Cochrane Review Group and peer reviewers, three previously included studies (Bergström 2005; Chatta 2008; Moriyama 2008) have been excluded from further updates. Whilst the authors of these three studies had provided data on women who were symptomatic at baseline, it was believed important for future updates to adhere to clear criteria of including only studies in which all women were symptomatic at baseline.

Therefore a grand total of five studies (nine reports) were eligible for inclusion in this 2014 update (Elavsky 2007; Hanachi 2008; Lindh-Åstrand 2004; Luoto 2012; Sternfeld 2014). The Elavsky 2007 study has one additional report (Elavsky 2009), the Luoto 2012 study has two additional reports (Mannsikkamaki 2012; Moilanen 2012) and the Sternfeld 2014 study has one additional report (Newton 2013) relevant to this review. Full descriptions of the included studies can be found under Characteristics of included studies.

Study design

All included trials were parallel-group randomised controlled trials (RCTs). They took place in Iran (Hanachi 2008), Sweden (Lindh-Åstrand 2004), USA (Elavsky 2007; Sternfeld 2014) and Finland (Luoto 2012). All studies appeared to be single-centre, except one (Sternfeld 2014).

Use of intention-to-treat analysis was clearly specified in three trials (Elavsky 2007; Luoto 2012; Sternfeld 2014).

Two studies stated that power calculations were used to statistically estimate the sample size (Luoto 2012; Sternfeld 2014).

Participants

The five included studies randomly assigned a total of 762 perimenopausal or postmenopausal women. Four trials (Hanachi 2008; Lindh-Åstrand 2004; Luoto 2012; Sternfeld 2014) determined menopausal status by measuring serum follicle-stimulating hormone levels and serum oestradiol levels. One trial determined menopausal status by examining self-reported bleeding patterns (Elavsky 2007). This trial reported that premenopausal women were also included in the sample (n = 17%), as determined by self-reported bleeding patterns. However, contact with study authors revealed that the bleeding history of women who initially reported no signs of the menopause transition based on bleeding criteria was verified before their entry into the trial (Elavsky 2007). All trials required that women were not using any hormone treatment (HT) at baseline.

All studies included only participants who were vasomotor symptomatic at baseline. Only two trials specified the length of time participants had been experiencing vasomotor symptoms before baseline. One trial (Elavsky 2007) recruited women who had been experiencing vasomotor symptoms in the last month before baseline, and another (Lindh-Åstrand 2004) recruited participants who had been vasomotor symptomatic for at least six months previously. In one trial (Sternfeld 2014), the frequency and bothersomeness of participants' vasomotor symptoms were measured before randomisation.

Four studies included women who were sedentary or had low activity at baseline (Elavsky 2007; Lindh-Åstrand 2004; Luoto 2012; Sternfeld 2014). One study excluded women who had been practicing yoga before baseline (Sternfeld 2014). One study did not state the baseline exercise levels of participants (Hanachi 2008).

In three trials (Elavsky 2007; Luoto 2012; Sternfeld 2014), participants were recruited after they responded to newspaper advertisements or to other media. One trial (Lindh-Åstrand 2004) recruited participants through a combination of newspaper advertisements and via gynaecology outpatient clinics. One study did not report the method used to recruit participants (Hanachi 2008).

Four trials (Elavsky 2007; Lindh-Åstrand 2004; Luoto 2012; Sternfeld 2014) reported generally comparable group demographic characteristics at baseline. One trial (Hanachi 2008) did not report the demographic characteristics of groups at baseline.

Interventions

Comparisons were as follows.

- Exercise (walking) versus yoga versus no intervention (Elavsky 2007).
- Exercise (aerobics) versus HT (Lindh-Åstrand 2004).
- Exercise (walking) plus soy milk consumption versus soy milk consumption only versus no intervention (Hanachi 2008).
- Exercise (cardiovascular conditioning) versus yoga versus usual activity, plus omega-3 or placebo pills in a 1:1 ratio within each group (Sternfeld 2014).
- Exercise (walking) versus controls, plus lectures once or twice per month on physical activity and general health in both arms (Luoto 2012).

Length of the interventions ranged from three (Hanachi 2008; Lindh-Åstrand 2004; Sternfeld 2014) to four (Elavsky 2007) to six months (Luoto 2012). Only two trials provided data on compliance with the intervention(s) (Elavsky 2007; Sternfeld 2014).

Outcomes

Vasomotor symptoms

All studies assessed vasomotor symptoms by self-report. One trial (Luoto 2012) assessed vasomotor symptoms by using more than one questionnaire/measure, but only one of the measures had been validated (the vasomotor symptoms subscale of the Women's Health Questionnaire). One study (Elavsky 2007) used the Greene Climacteric Scale (Greene 1998). Two studies (Hanachi 2008; Lindh-Åstrand 2004) used the Kupperman Index (Kupperman 1959), although one study (Lindh-Åstrand 2004) did not report data specifically from the vasomotor symptoms subscale. Two studies (Lindh-Åstrand 2004; Luoto 2012) used a log/diary to assess

the number and/or severity of hot flushes at baseline and at follow-up.

Adverse events

One study (Sternfeld 2014) assessed adverse events.

Data extraction

Data from all trials, except one (Hanachi 2008), were entered into the meta-analysis. One study produced binary data (Hanachi 2008), and four studies produced continuous data (Elavsky 2007; Lindh-Åstrand 2004; Luoto 2012; Sternfeld 2014). One study included both continuous (primary outcome) and binary data (secondary outcome). In the meta-analyses, we used data from the final follow-up, regardless of time since baseline.

Length of follow-up varied considerably between studies, ranging from three months (Hanachi 2008; Sternfeld 2014) to six months (Luoto 2012) to nine months (Lindh-Åstrand 2004) to 24 months (Elavsky 2007).

Excluded studies

In 2007, on the basis of information provided in the abstract, one study was not traceable by the British Library (Pangaotopulos 2004) despite numerous search attempts. Eight reports were not RCTs (Hammar 1990; Kemmler 2004; Salmone 1998; Slaven 1994; Wallace 1982; Weltman 1982; Ueda 2000; Ueda 2004). Eight reports did not include women who were symptomatic at baseline (Aiello 2004; Boraz 2001; Hunter 1999; Krasnoff 1996; Liao 1998; Polis 1989; Steele 1997; Wilbur 2005); we were unable to obtain data for women in these trials who were symptomatic, and we were unable to reach the trial authors or the authors were unable to provide data in a usable form for this review. For further details, see the Characteristics of excluded studies tables.

Further studies were identified as ineligible during the process of updating the 2011 review (first update). Five reports were not RCTs (Booth-LaForce 2007; Cohen 2006; Elavsky 2005; Lee 2009; McAndrew 2009), four reports did not include vasomotor symptomatic women at baseline (Asbury 2006; Gonzalez 2009; Maesta 2007; Villaverde 2006b), one report did not include an exercise intervention (Welty 2007) and one report did not include a measure of vasomotor symptoms (O'Donnell 2009).

In this 2014 update of the review, a further 15 studies were retrieved and excluded for the following reasons: duplicate abstract of another study (Cramer 2012b); no measure of vasomotor symptoms (Foster-Schubert 2012; Kline 2012; Kok 2005; Lee 2012; Riesco 2012; Villaverde-Gutiérrez 2012); unclear whether participants were vasomotor symptomatic at baseline (Llaneza 2011; Riesco 2011); participants were not vasomotor symptomatic at baseline (Alfonso 2012; Joshi 2011; Ogwumike 2011); trials were not RCTs (Garcia 2011); and participants were taking HT at baseline (Huang 2010; Moreira 2012). As discussed earlier, in this second update of the review (2014), it was decided that the studies by Bergström 2005, Chatta 2008 and Moriyama 2008 that had been included in the 2010 review should be excluded from any subsequent updates, including this one, as not all randomly assigned participants were symptomatic at baseline.

Risk of bias in included studies

For further details, refer to the methodological quality summary (Figure 2) and the methodological quality graph (Figure 3).

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

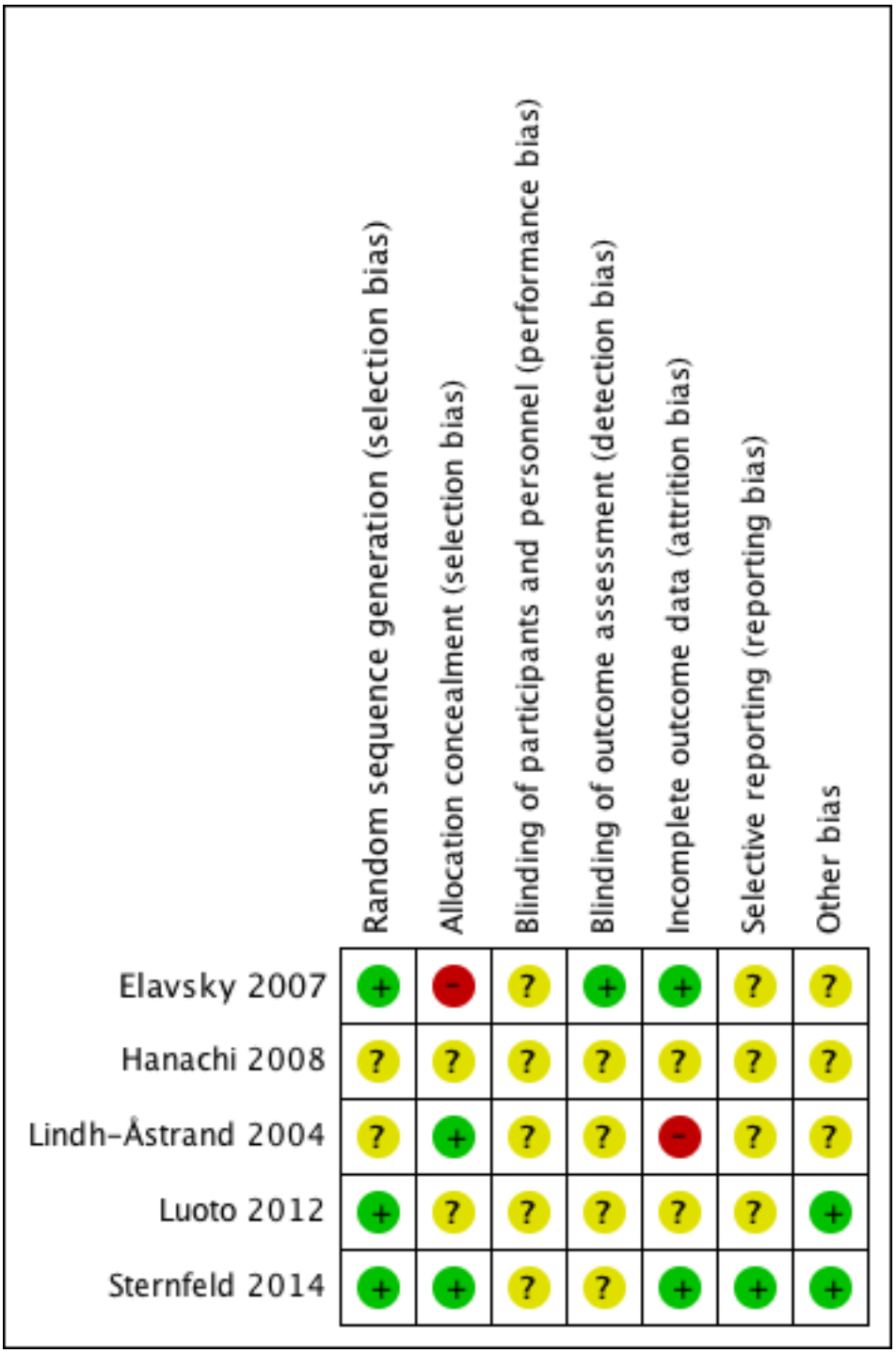
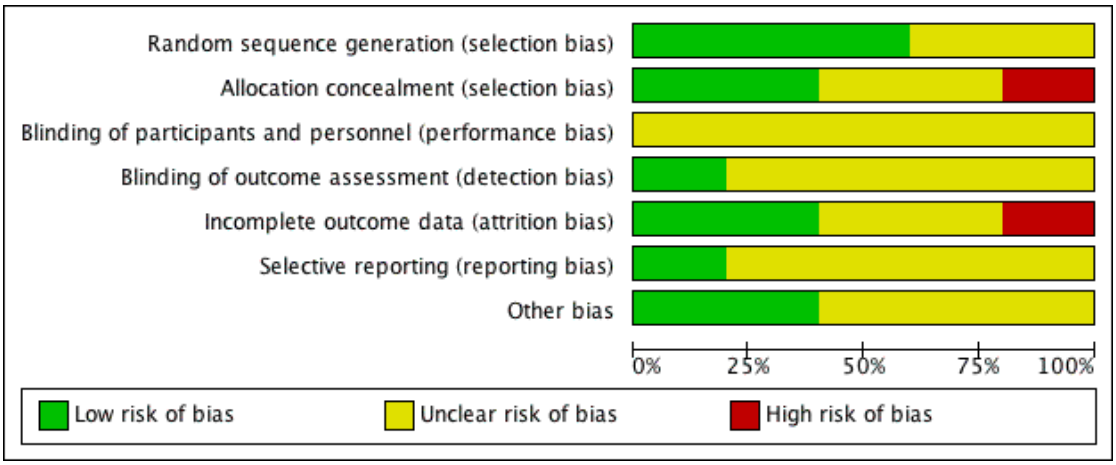


Figure 3. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Allocation

Three studies reported adequate methods of sequence generation (Elavsky 2007; Luoto 2012; Sternfeld 2014). They used computer-generated lists. Two trials did not specify this information and were rated as having unclear risk in this domain (Hanachi 2008; Lindh-Åstrand 2004).

Two studies provided evidence of adequate allocation concealment (Lindh-Åstrand 2004; Sternfeld 2014); presealed envelopes, identical opaque sealed envelopes or a secure Web-based database was used. Two studies provided insufficient information as to whether allocation was concealed and were rated as having unclear risk in this domain (Hanachi 2008; Luoto 2012). Contact with the trial authors revealed that allocation was not concealed in one trial (Elavsky 2007); this study was rated as having high risk of bias in this domain.

Blinding

Evaluation of exercise-based treatment is more difficult than evaluation of other types of treatment such as pharmacological interventions because usually neither the participant nor the intervener can be blinded to participants' allocation; comments here should be interpreted in light of these constraints. Two trials clearly stated that outcome assessors were blinded to group allocation and were rated as having low risk of bias in this domain (Elavsky 2007; Sternfeld 2014). The other studies were rated as having unclear risk of bias.

Incomplete outcome data

Two trials adequately addressed this domain and were rated as having low risk of bias (Elavsky 2007; Sternfeld 2014). One trial had a high attrition rate and was rated as having high risk of bias (Lindh-Åstrand 2004), and in two trials, the risk of bias was unclear (Hanachi 2008; Luoto 2012). Please see Characteristics of included studies for details.

Selective reporting

Only one trial reported adverse events (Sternfeld 2014) and was rated as having low risk of bias in this domain. The other studies were rated as having unclear risk of selective reporting bias.

Other potential sources of bias

No other potential source of bias was identified for two trials (Luoto 2012; Sternfeld 2014), which were rated as having low risk in this domain. Three trials were rated as having unclear risk of bias in this domain as a result of lack of baseline equivalence between groups (Elavsky 2007), poor reporting (Hanachi 2008) or high rates of cross-over between treatment arms (Lindh-Åstrand 2004).

Effects of interventions

See: **Summary of findings for the main comparison** Exercise versus control for vasomotor menopausal symptoms; **Summary**

of findings 2 Exercise versus yoga for vasomotor menopausal symptoms

Three meta-analyses were conducted: exercise versus no treatment/control, exercise versus yoga and exercise versus HT. In the five included studies, a total of 762 participants were randomly assigned, but data from one study (Hanachi 2008) (n = 37) could not be included in any meta-analysis. Therefore data from 725 randomly assigned participants were eligible for inclusion in the meta-analyses, and of these, 605 provided follow-up data (83.4%).

1 Exercise versus no treatment/control

Four trials were eligible for inclusion in the comparison of exercise versus no treatment or a control condition.

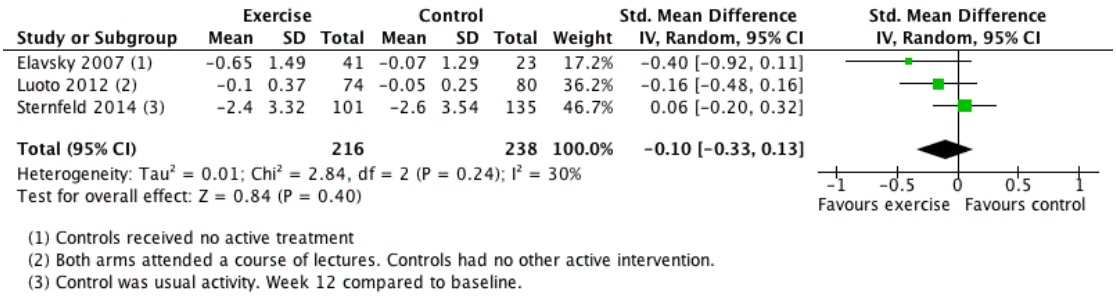
Three studies compared exercise (walking (Elavsky 2007), aerobic exercise (Luoto 2012) and cardiovascular training (Sternfeld 2014)) versus no intervention. A fourth study (Hanachi 2008) compared exercise plus soy milk versus soy milk alone or a control condition (not described). No direct comparison was performed between the two intervention groups.

Primary outcome

1.1 Frequency or intensity of vasomotor menopausal symptoms

When three studies were pooled (Elavsky 2007; Luoto 2012; Sternfeld 2014), no evidence suggested a difference between groups (standardised mean difference (SMD) -0.10, 95% confidence interval (CI) -0.33 to 0.13, 454 participants, I^2 = 30%, low-quality evidence) (Figure 4 Analysis 1.1). Hanachi 2008 reported data unsuitable for pooling. Thirty-seven women were included in the analysis. The study authors stated that hot flush scores decreased significantly during the treatment period in the exercise plus soy milk group and in the soy milk only group, relative to the control group (P value < 0.05). See Analysis 1.2 for details.

Figure 4. Forest plot of comparison. Exercise versus control, outcome: 1.1 Change in hot flushes/night sweats.



(1) Controls received no active treatment
(2) Both arms attended a course of lectures. Controls had no other active intervention.
(3) Control was usual activity. Week 12 compared to baseline.

Secondary outcomes

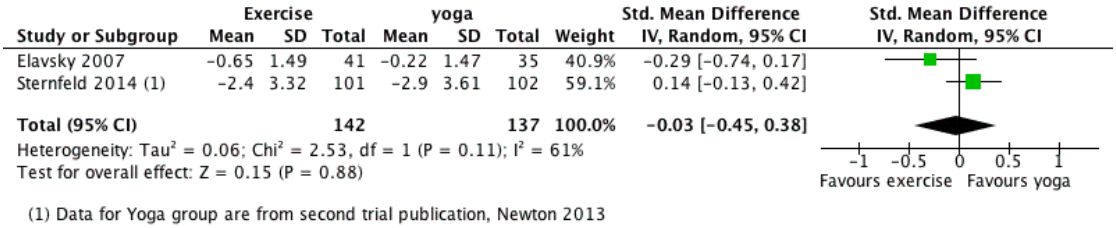
1.2 Adverse effects of the intervention

The number of incident adverse events was reported in one trial (Sternfeld 2014) and was similar in both groups (17% for exercise and 18% for usual activity); no serious adverse events related to the study occurred in either group.

2 Exercise versus yoga

Two studies were included in this analysis (Figure 5 Analysis 2.1). These trials compared exercise (walking) (Elavsky 2007) and cardiovascular training (Sternfeld 2014) versus yoga.

Figure 5. Forest plot of comparison. Exercise versus yoga, outcome: 1.2 Change in hot flushes/night sweats.



(1) Data for Yoga group are from second trial publication, Newton 2013

Primary outcome

2.1 Frequency or intensity of vasomotor menopausal symptoms

When the two studies were pooled, no evidence showed a difference between groups (SMD 0.03, 95% CI -0.45 to 0.38, 279 participants, I^2 = 61%, low-quality evidence).

Secondary outcomes

2.2 Adverse effects of the intervention

No serious adverse events were reported for either group.

3 Exercise versus hormone therapy (HT)

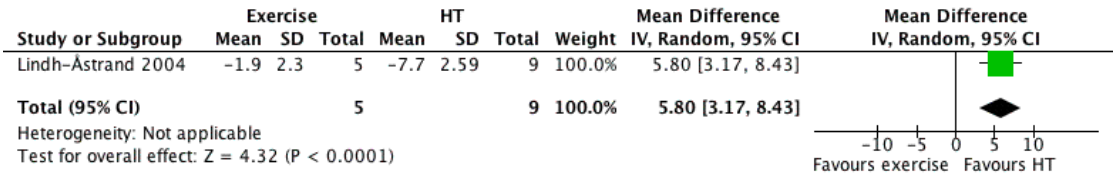
One trial compared exercise (aerobics) versus HT (Lindh-Åstrand 2004).

Primary outcome

3.1 Frequency or intensity of vasomotor menopausal symptoms

In this trial (Lindh-Åstrand 2004) at 12 weeks' follow-up, a larger reduction in frequency of hot flushes per 24 hours was seen in the HT group than in the exercise group (mean difference 5.80, 95% CI 3.17 to 8.43, 14 participants) (Figure 6; Analysis 3.1).

Figure 6. Forest plot of comparison. 3 Exercise versus HT, outcome: 3.1 Change in mean number of flushes in 24 hours.



Secondary outcomes

3.2 Adverse effects of the intervention

Data on adverse effects of the intervention were not reported in the only trial included in this comparison.

Sensitivity analyses

Only one study was deemed to have low risk of bias (Sternfeld 2014). Exclusion from analysis of other studies did not affect our overall findings for any outcome.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Exercise versus yoga for vasomotor menopausal symptoms

Population: women with vasomotor menopausal symptoms

Intervention: exercise versus yoga

Outcomes	Illustrative comparative risks* (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Corresponding risk			
	Exercise versus yoga			
Change in hot flushes/ night sweats Self-report Follow-up: 3 to 4 months	Mean change in hot flushes/night sweats **0.03 standard deviations lower in the exercise groups** (-0.45 lower to 0.38 higher)	279 (2 studies)	⊕◯◯◯ **Low**[a,b,c]	SMD -0.03 (-0.45 to 0. 38)

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a] Evidence self-reported: validated scales or logs/diaries used.
[b] Recruitment, method of determining menopausal status and characteristics of included women varied.
[c] Variation in the direction of effect ($I^2 = 61\%$).

DISCUSSION

Summary of main results

Evidence was insufficient to show whether exercise is an effective treatment for vasomotor menopausal symptoms. Evidence was also insufficient to reveal the relative effectiveness of exercise when compared with HT or yoga. The evidence was of low quality because of observed limitations in study design, inconsistency and imprecision.

The two largest trials to date (Luoto 2012; Sternfeld 2014) showed no significant differences between exercise and control groups for their primary outcome of vasomotor symptoms. These results should also be considered in the context of intervention contamination, which is often a problem with exercise trials, as comparator/usual care groups may spontaneously choose to exercise,

thereby diluting the effect. This issue might have been a particular problem in one of the larger included trials (Luoto 2012), in which the control group was given lectures on physical activity, thus providing encouragement for them to exercise. Although the RCOG (RCOG 2006) has advised that regular aerobic exercise may help relieve menopausal symptoms, the most common of which is hot flushes, current evidence does not support this statement. Additional high-quality trials are required before conclusions can be drawn about the effectiveness of exercise compared with no treatment or active interventions such as yoga or HT. Evidence of heterogeneity is also apparent in the meta-analysis of exercise versus yoga, highlighting further the need for additional research.

Overall completeness and applicability of evidence

Data regarding adverse effects of exercise interventions are insufficient, and not all studies reported data in a form that could be included in the meta-analysis.

Quality of the evidence

The methodological quality of studies was variable, and only one trial (Sternfeld 2014) was at low risk of bias. In the comparisons of exercise versus control/no treatment, 30% heterogeneity was evident, whereas in the comparison of exercise versus yoga, heterogeneity was high (61%), possibly because of differences between studies in intensity of the interventions.

Sample sizes in both meta-analyses were relatively small. Some study authors did not follow the CONSORT (Consolidated Standards of Reporting Trials) guidelines in reporting their studies; this often made it difficult for review authors to extract and interpret the information required for this review. Studies also varied considerably by type and duration of the exercise intervention and length of follow-up.

We assessed the evidence as low quality: Limitations in study design, inconsistency and imprecision were noted. Methods of recruitment and of determining menopausal status varied, as did characteristics of included women. Evidence was self-reported on a variety of validated scales or logs/diaries. Both meta-analyses showed variation in the direction of effect.

Potential biases in the review process

Publication and selection biases are potential threats to all systematic reviews. We believe that all relevant studies have been identified but cannot rule out the possibility that additional trials may be unpublished or published in sources not accessible to our search.

Agreements and disagreements with other studies or reviews

We are not aware of any other published reviews of randomised controlled trials that have assessed the effectiveness of exercise as a treatment for vasomotor menopausal symptoms.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence was insufficient to show whether exercise is an effective treatment for vasomotor menopausal symptoms. Evidence was also insufficient to reveal the relative effectiveness of exercise and yoga. One small study suggested that HT is more effective than exercise.

Implications for research

Additional high-quality trials of exercise versus no exercise or in comparison with other types of interventions would be welcome. Studies should evaluate not just the outcomes of frequency and intensity of vasomotor symptoms, but also whether adverse events are associated with exercise. Cost/benefit analyses should be included. Adherence has not been detailed in reports or has not been reported in sufficient detail to show how much exercise women were performing throughout the interventions. Future trials should measure and report adherence in greater detail.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Elavsky 2007

Methods	3-group RCT: exercise, yoga, control
Participants	Low active or sedentary women 42 to 58 years of age who were experiencing vasomotor menopausal symptoms in the past month and had no history of surgical menopause and no hormone therapy use in the previous 6 months A total of 164 participants were randomly assigned (exercise n = 63, yoga n = 62, control n = 39). At four-month follow-up, 16 were lost to follow-up (exercise n = 6, yoga n = 7, control n = 3). However, only 1 participant (yoga group) was excluded from the analyses (used HT); thus 163 participants were included in the analyses (161 for primary outcome). At 2-year follow-up, data were available for 134/164 randomly assigned participants. Of these, 102/134 agreed to take part in the 2-year follow-up study and 99/134 returned a follow-up questionnaire (response rate of 74%; 99/134) (exercise n = 41, yoga n = 35, control n = 23). Overall, 60.4% (99/164) provided follow-up questionnaire data 2 years after randomisation
Interventions	• The exercise intervention involved a low to moderate supervised walking programme. Participants met 3 times per week for 1 hour at a university centre. Participants were also encouraged to add 1 to 2 days of exercise outside of the supervised programme. Participants received individualised exercise prescriptions, as well as educational leaflets, handouts and newsletters • The yoga (Iyengar) group met twice per week for 90 minutes. Sessions were supervised by an instructor. Iyengar yoga places particular emphasis on developing strength, stamina, flexibility and balance, as well as concentration and meditation. Participants were also encouraged to practice postures outside of the supervised programme, following handouts received on a weekly basis • Wait list control The intervention period was 4 months
Outcomes	Vasomotor menopausal symptoms using the Greene Climacteric Scale. Adverse events were not reported
Notes	Inclusion criteria stipulated that women had to be vasomotor symptomatic at baseline, but results indicate that based on classification of bleeding patterns (by self-report), 17% of participants would be considered premenopausal Most of the sample (70%) were overweight or obese More participants were purposefully randomly assigned to the exercise (n = 63) and yoga (n = 62) groups than to the control group (n = 39). Trial authors intentionally oversampled in the exercise and control groups to increase the probability of detecting a difference between outcomes in these groups, and because resources for physician cover for physiological testing were limited in the control group Intervention compliance: Compliance between yoga (63%) and exercise (70%) groups did not differ significantly during the 4-month intervention period. At 2-year follow-up, physical activity was assessed in terms of energy expenditure/METs per week, but no data according to group were reported

Elavsky 2007 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned to trial groups by a computer-based statistical package
Allocation concealment (selection bias)	High risk	Contact with trial authors indicates that allocation was not concealed from the research team
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It is not possible to blind exercise interventions to participants nor to trial personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study states that all medical and testing staff were blind to group allocation at outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	161/164 women were analysed for the primary outcome
Selective reporting (reporting bias)	Unclear risk	Study does not report adverse events
Other bias	Unclear risk	Trial groups were not balanced at baseline with regard to age, socioeconomic status and number of children. High rate of refusal to participate among eligible women (204/462 refused) could potentially affect applicability of findings

Hanachi 2008

Methods	3-group RCT: exercise plus soy milk (n = 12 analysed), soy milk only (n = 15 analysed) and control (n = 10 analysed) Study authors analysed 37 participants (exercise plus soy milk n = 12; soy milk only n = 15; control n = 10), but no data regarding dropouts or loss to follow-up were reported. Study authors did not respond to our request for further information regarding loss to follow-up. Therefore it is unclear how many women were randomly assigned
Participants	Non-smoking postmenopausal women, free from disease, not taking any form of hormone treatment in the previous 12 months and not currently using soybean-derived products or herbal medications, with intact uterus and experiencing hot flushes
Interventions	• Exercise intervention involved 1 hour of walking each day + soy milk • Soy milk only • Control (intervention not described)
Outcomes	Vasomotor menopausal symptoms assessed using the Kupperman Index. Adverse events not reported

Hanachi 2008 (*Continued*)

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study states it is a randomised trial and provides no other details
Allocation concealment (selection bias)	Unclear risk	No information was given in the trial report to allow a judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It is not possible to blind exercise interventions to participants or to trial personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Reports of the trial do not state whether outcome assessors were blinded from knowledge of which intervention participants received
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It is unclear whether the 37 women analysed included all who were randomly assigned
Selective reporting (reporting bias)	Unclear risk	Outcomes were reported in narrative form and on graphs; no raw data were suitable for analysis. Adverse events were not reported
Other bias	Unclear risk	Poor reporting: Control intervention was not described. Baseline characteristics are similar in the 2 groups

Lindh-Åstrand 2004

Methods	2-group RCT: exercise, HT
Participants	Women 48 to 63 years, with vasomotor symptoms and spontaneous menopause at least 6 months previously and exercising less than 1 hour per week at baseline. Contact with the study author revealed that participants were not taking HT at baseline Study originally included 75 women who were randomly assigned to exercise, 2 modes of acupuncture, oestrogen therapy (HT) or applied relaxation (n = 15 per group). We describe data here from the report that compared exercise with HT (Lindh-Åstrand 2004). Results from the other groups are presented elsewhere (Nedstrand 2005; Wyon 2004), but none of these are compared with exercise. Of women randomly assigned to exercise, 4/15 did not start the exercise programme, and 1 participant dropped out during the intervention, resulting in 10/15 receiving follow-up at 12 weeks. Only 5

	of the participants randomly assigned to exercise completed follow-up at 24 week and 36 weeks. Among women randomly assigned to HT (n = 15), all completed follow-up at 12 weeks, and 9/15 completed 24-week follow-up. It is not entirely clear from the report how many women in the HT completed follow-up at 9 months, but it appears to be 9/15. In summary, 14 participants provided follow-up data at 24 weeks; therefore the Lindh-Åstrand 2004 trial was judged likely to contain high attrition bias because dropout at follow-up was substantial
Interventions	• Exercise group participated in 60-minute aerobic classes of moderate intensity at a university centre for 12 weeks. Women had to attend at least 2 classes every week and to spend at least 1 additional hour/wk participating in exercise of such intensity that a shower was required afterwards • HT group was given unopposed 17β-oestradiol 2 mg orally per day for 12 weeks. Thereafter it was suggested that they continue their oestrogen treatment with additional sequential progestogens given monthly
Outcomes	Number of hot flushes per 24 hours using a diary/log book. Climacteric symptoms assessed by the Kupperman Index, although scores for vasomotor symptoms subscale were not reported Total climacteric symptom intensity and distress experienced from symptoms, although this outcome was not vasomotor symptom specific and was focused on all menopausal symptoms
Notes	This trial report is part of a larger trial in which women were also randomly assigned to 3 other treatment groups; data from these groups are reported separately

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Study reports it is a randomised trial and provides no other details
Allocation concealment (selection bias)	Low risk	Randomisation was performed with the use of identical, opaque, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It is not possible to blind exercise interventions to participants or to trial personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Reports of the trial do not state whether outcome assessors were blinded from knowledge of which intervention participants received
Incomplete outcome data (attrition bias) All outcomes	High risk	Data are incomplete for all outcomes and were unbalanced across groups at each follow-up. Reason for missing data is likely to be related to true outcome. Only 10/15 (66%) women in exercise arm were included in the analysis

Lindh-Åstrand 2004 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Adverse effects were not reported
Other bias	Unclear risk	High rate of cross-overs was seen in the exercise arm-only 5 women completed protocol and follow-up; 5/10 included in analysis started HT during study

Luoto 2012

Methods	2-group RCT: exercise vs control
Participants	Symptomatic women experiencing daily hot flushes, 40 to 63 years of age, not taken HT in the previous 3 months, sedentary and 6 to 36 months since less menstruation. All participants were of white ethnicity Study randomly assigned 176 women equally to the exercise group or the control group; 154 received follow-up (exercise group n = 74; control group n = 80). Both trial groups received 1-hour lectures once or twice per month from the principal investigator on physical activity and general health
Interventions	• Six-month unsupervised aerobic exercise training programme that included aerobic training 4 times per week for 50 minutes at moderate to hard intensity. At least 2 sessions per week needed to include walking or nordic walking • Women in the control group were asked (via questionnaire on paper) once in the middle of the trial (11-12 weeks from baseline) whether they had changed any of their physical activities or dietary habits All participants also attended lectures (60-75 minutes) once or twice per month, which covered topics such as physical activity and general health
Outcomes	Vasomotor symptoms measured by the Women's Health Questionnaire. Hot flushes and night sweats recorded by diary. Adverse events not reported
Notes	Control group attended lectures once or twice per month, which covered topics such as physical activity and general health

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation list was computer generated
Allocation concealment (selection bias)	Unclear risk	Envelopes were used to randomly assign participants, but no details were provided about whether they were sealed or consecutively numbered
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information about blinding is given

Luoto 2012 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information about blinding is given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	154/176 (88%) women were included in the analysis. Dropouts were potentially related to efficacy or adverse effects (e.g. 2 dropouts in exercise group crossed over to HT, 2 dropped out because of musculoskeletal problems, no reason was given for 9). Significant differences in age and weight were noted between dropouts and non-dropouts
Selective reporting (reporting bias)	Unclear risk	Adverse effects were not reported
Other bias	Low risk	This study appears free of other sources of bias

Sternfeld 2014

Methods	3-group RCT: exercise, yoga and usual care control group
Participants	Women 42 to 62 years of age, late perimenopausal or postmenopausal or having a hysterectomy with FSH > 20 mIU/mL and oestradiol ≥ 50 pg/mL. To be eligible, women must have been experiencing 14 or more vasomotor symptoms per week in each of 3 consecutive weeks, as measured by daily diaries. Vasomotor symptom frequency between visits 1 and 2 no less than 50% of weekly mean in the 2 weeks before Visit 1, and symptoms rated as severe or bothersome on at least 4 occasions. Women taking HT or contraceptives in past 2 months were excluded, as were women with BMI > 37. Women taking omega-3 and participating in yoga in the previous 3 months were excluded 355 women were randomly assigned to exercise (n = 106), usual activity (n = 142) or yoga (n = 107). Of these, 338 received follow-up (exercise n = 101, yoga n = 102, control group n = 135)
Interventions	• Exercise intervention consisted of 12 weeks of 3 individualised cardiovascular training sessions per week at a local leisure centre supervised by an exercise trainer. The intervention was progressive over time, from moderate to hard intensity. Sessions lasted between 40 and 60 minutes • Usual activity: This group was asked to refrain from changing physical activity behaviour during the trial • The yoga intervention involved the practice of cooling breathing exercises and 3 groups of poses (asanas). Poses were sequenced according to the principles of viniyoga to promote safety Women were further randomly assigned (1:1) within each arm to 1.8 g/d U-3 fish oil or identically appearing placebo capsules
Outcomes	Vasomotor symptom frequency as measured by daily diaries. Bother of symptoms as measured by daily diaries. Adverse events reported for both groups

Notes	This was a multi-site trial. Data for the yoga group were extracted for this review from the second trial publication (Newton 2013) Intervention compliance: Participants attended 8.5 (3.5) (mean (SD)) of 12 scheduled yoga sessions (ranging from 0 to 13). Women practiced at home 4.1 (2.3) times per week. On average, women did poses 2.6 (1.1) times per week and Yoga Nidra 2.3 (1. 2) times per week. Adherence to the exercise intervention was assessed in several ways: attendance at 80% or more of training sessions; achievement of 80% or more of weekly energy expenditure goal; and achievement of target heart rate (+10 beats/min) for 50% or more of exercise time. Documented home-based training sessions were counted for women who were unable to attend a facility-based session. Study authors reported that 74 women adhered to the intervention (defined by training sessions), 66 women achieved the energy expenditure goal and 75 achieved the target heart rate goal. Activity behaviour outside exercise training decreased by 1.5 steps/min in the exercise group compared with an increase of 0.22 steps/min in the usual activity group (P value 0.02)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated dynamic randomisation algorithm was used to maintain comparability between groups
Allocation concealment (selection bias)	Low risk	Randomisation was conducted using a secure Web-based database
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Data collectors were blinded to participants' group allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Local access to information on group assignment was limited to site staff involved in delivery of the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	241/248 (97%) women in exercise vs usual care group and 237/249 in yoga vs usual care group (95%) were included in the analysis
Selective reporting (reporting bias)	Low risk	Report includes all expected outcomes and data on adverse events
Other bias	Low risk	Women were further randomly assigned (1: 1) within each arm to 1.8 g/d U-3 fish oil or identically appearing placebo capsules. This appears unlikely to be associated with bias

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aiello 2004	Not all participants were symptomatic at baseline
Alfonso 2012	Participants were not vasomotor symptomatic at baseline
Asbury 2006	Participants were not vasomotor symptomatic at baseline
Bergström 2005	Not all participants were symptomatic at baseline
Booth-LaForce 2007	Not an RCT
Boraz 2001	Not all participants were vasomotor symptomatic at baseline
Chatta 2008	Not all participants were symptomatic at baseline
Cohen 2006	Not an RCT
Cramer 2012b	Nor an RCT
Elavsky 2005	Not an RCT
Foster-Schubert 2012	No measure of vasomotor symptoms
Garcia 2011	Not an RCT
Gonzalez 2009	Participants were not vasomotor symptomatic at baseline
Hammar 1990	Case control study
Huang 2010	12.3% of participants were taking HT at baseline. Not possible to obtain data for those participants not taking HT at baseline
Hunter 1999	29% of participants were taking HT at the time of the study. Not clear whether all participants were vasomotor symptomatic at baseline
Joshi 2011	Participants were not vasomotor symptomatic at baseline
Kemmler 2004	Not an RCT
Kline 2012	No measure of vasomotor symptoms
Kok 2005	No measure of vasomotor symptoms
Krasnoff 1996	Not clear whether all participants were symptomatic at baseline, and the study author could not be located for clarification

(*Continued*)

Lee 2009	Not an RCT (systematic review)
Lee 2012	No measure of vasomotor symptoms
Liao 1998	Not all participants were symptomatic at baseline
Llaneza 2011	Unclear whether participants were symptomatic at baseline
Maesta 2007	Participants were not vasomotor symptomatic at baseline
McAndrew 2009	Not an RCT
Moreira 2012	Most participants were taking HT at baseline
Moriyama 2008	Not all participants were symptomatic at baseline
O'Donnell 2009	No measure of vasomotor symptoms
Ogwumike 2011	Participants were not vasomotor symptomatic at baseline
Pangaotopulos 2004	Study not traceable by the British Library
Polis 1989	Not all participants were symptomatic at baseline
Riesco 2011	Unclear whether participants were symptomatic at baseline
Riesco 2012	No measure of vasomotor symptoms
Salmone 1998	Not an RCT
Slaven 1994	Not an RCT
Steele 1997	Not all participants were symptomatic at baseline
Ueda 2000	Not an RCT
Ueda 2004	Not an RCT
Villaverde 2006b	Participants were not vasomotor symptomatic at baseline
Villaverde-Gutiérrez 2012	No measure of vasomotor symptoms
Wallace 1982	Not an RCT
Weltman 1982	Not an RCT
Welty 2007	Did not include an exercise intervention

(*Continued*)

Wilbur 2005	Not all participants were symptomatic at baseline

Characteristics of ongoing studies *[ordered by study ID]*

Daley 2013

Trial name or title	Aerobic exercise as a treatment for vasomotor menopausal symptoms: randomised controlled trial
Methods	RCT
Participants	261 inactive perimenopausal and menopausal symptomatic women not using HT
Interventions	2 exercise interventions: (1) exercise consultations plus DVD and written literature; (2) exercise consultations plus exercise social support groups
Outcomes	Hot flushes, night sweats, other menopausal symptoms, quality of life, depression, anxiety
Starting date	January 2012
Contact information	a.daley@bham.ac.uk
Notes	Principal investigator of this trial is also the first author of this review

DATA AND ANALYSES

Comparison 1. Exercise versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in hot flushes/night sweats	3	454	Std. Mean Difference (IV, Random, 95% CI)	-0.10 [-0.33, 0.13]
2 Additional data: decrease in hot flushes			Other data	No numeric data

Comparison 2. Exercise versus yoga

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in hot flushes/night sweats	2	279	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-0.45, 0.38]

Comparison 3. Exercise versus HT

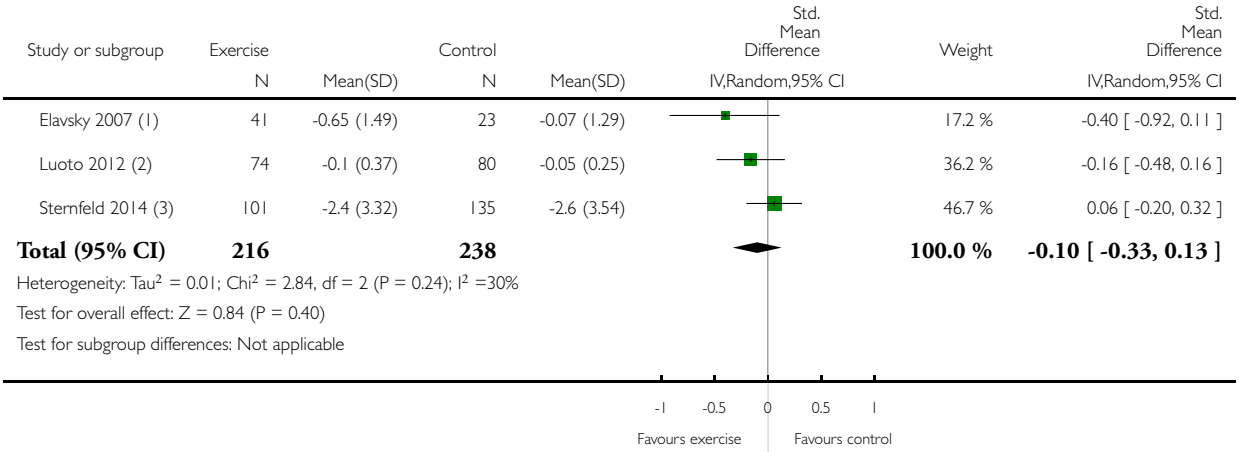
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in mean number of flushes in 24 hours	1	14	Mean Difference (IV, Random, 95% CI)	5.80 [3.17, 8.43]

Analysis 1.1. Comparison 1 Exercise versus control, Outcome 1 Change in hot flushes/night sweats.

Review: Exercise for vasomotor menopausal symptoms

Comparison: 1 Exercise versus control

Outcome: 1 Change in hot flushes/night sweats



(1) Controls received no active treatment

(2) Both arms attended a course of lectures. Controls had no other active intervention.

(3) Control was usual activity. Week 12 compared to baseline.

Analysis 1.2. Comparison 1 Exercise versus control, Outcome 2 Additional data: decrease in hot flushes.

Additional data: decrease in hot flushes

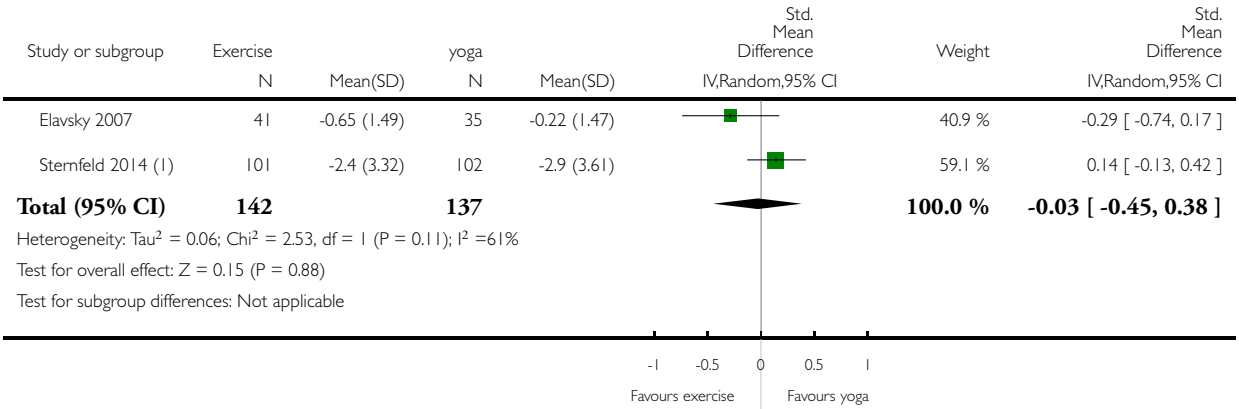
Study	Outcome	Intervention	Comparison	Result	Statistical significance
Hanachi 2008	Decrease in hot flushes	1. Exercise + soymilk	2. Soymilk only 3. Control (no details)	Group 1. Hot flushes decreased by 83% relative to Group 3 Group 2. Hot flushes decreased by 72% relative to Group 3	Significant benefit for Group 1 and Group 2 versus Group 3 p<0.05

Analysis 2.1. Comparison 2 Exercise versus yoga, Outcome 1 Change in hot flushes/night sweats.

Review: Exercise for vasomotor menopausal symptoms

Comparison: 2 Exercise versus yoga

Outcome: 1 Change in hot flushes/night sweats



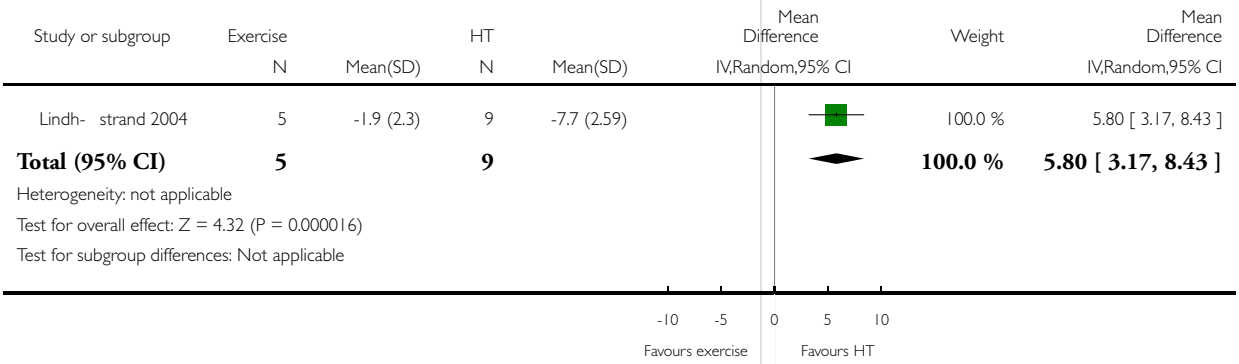
(1) Data for Yoga group are from second trial publication, Newton 2013

Analysis 3.1. Comparison 3 Exercise versus HT, Outcome 1 Change in mean number of flushes in 24 hours.

Review: Exercise for vasomotor menopausal symptoms

Comparison: 3 Exercise versus HT

Outcome: 1 Change in mean number of flushes in 24 hours



APPENDICES

Appendix 1. MDSG search strategy

MDSG search string last searched 03.04.14

Keywords CONTAINS “vasomotor” or “vasomotor symptoms” or “hot flashes” or “hot flushes” or “night sweats” or “night sweats-outcome” or “Flushes” or “Flushing” or “flushing outcome” or “climacteric ”or “climacteric symptoms” or “climacteric symptoms-outcome” or “climacteric symptoms - vasomotor” or “menopausal symptoms” or “*Menopause” or “ Title CONTAINS” vasomotor“ or ”vasomotor symptoms“ or ”hot flashes“ or ”hot flushes“ or ”night sweats“ or ”night sweats-outcome“ or ”Flushes“ or ”Flushing“ or ”flushing outcome“ or ”climacteric “ or ”climacteric symptoms“ or ”climacteric symptoms-outcome“ or ”climacteric symptoms - vasomotor“ or ”menopausal symptoms“ or”*Menopause“

AND

Keywords CONTAINS ”exercise“ or ”Exercise Therapy“ or ”yoga“ or ”walking“ or ”aerobic exercise“ or Title CONTAINS ”exercise“ or ”Exercise Therapy“ or ”yoga“ or ”walking“ or ”aerobic exercise“

Appendix 2. Search strategies

Database: PsycINFO <1806 to February Week 4 2014>
Search strategy:
1 exp Physical Education/ (3154)
2 exp Physical Fitness/ (3030)
3 exp Exercise/ or exp Aerobic Exercise/ (16253)
4 (physical$ or training or exercise$).tw. (393121)
5 (yoga or tai chi or tai ji or walking or running or jogging or swimming or cycling or bicycling).tw. (29621)
6 exp Yoga/ (954)
7 exp Walking/ (3224)
8 exp Running/ (1394)
9 exp Swimming/ (1348)
10 aerobic.tw. (2587)
11 fitness.tw. (10692)
12 or/1-11 (421747)
13 (flush$ or flash$ or sweat$ or vasomotor).tw. (10418)
14 exp Menopause/ (2863)
15 (menopaus$ or perimenopaus$ or postmenopaus$).tw. (4881)
16 climacter$.tw. (441)
17 or/13-16 (15055)
18 12 and 17 (2048)
19 random.tw. (39815)
20 control.tw. (309344)
21 double-blind.tw. (17649)
22 clinical trials/ (7328)
23 placebo/ (3706)
24 exp Treatment/ (570434)
25 or/19-24 (870514)
26 18 and 25 (747)
27 limit 26 to yr=”2013 -Current“ (39)
Database: EMBASE <1980 to 2014 Week 09>
Search strategy:
1 exp physical education/ (10109)
2 exp training/ (58544)
3 (physical$ or training or exercise$).tw. (979676)
4 exp fitness/ (27677)

5 exp exercise/ or exp aerobic exercise/ or exp stretching exercise/ (205535)
6 (yoga or tai chi or tai ji or walking or running or jogging or swimming or cycling or bicycling).tw. (157806)
7 exp yoga/ (3683)
8 exp Tai Chi/ (1354)
9 exp walking/ (60510)
10 exp running/ (15401)
11 exp swimming/ (14918)
12 exp bicycle/ (6032)
13 aerobic.tw. (64048)
14 fitness.tw. (45085)
15 or/1-14 (1265195)
16 (flush$ or flash$ or sweat$ or vasomotor).tw. (75639)
17 exp hot flush/ (11365)
18 exp flushing/ (13004)
19 (menopaus$ or perimenopaus$ or postmenopaus$).tw. (90733)
20 exp climacterium/ (7176)
21 exp menopause/ or exp menopause related disorder/ or exp "menopause and climacterium"/ (99278)
22 exp early menopause/ (1561)
23 exp postmenopause/ (44450)
24 climacter$.tw. (4791)
25 vasomotor.tw. (12406)
26 or/16-25 (207997)
27 15 and 26 (18964)
28 Clinical Trial/ (893833)
29 Randomized Controlled Trial/ (368808)
30 exp randomization/ (65021)
31 Single Blind Procedure/ (19116)
32 Double Blind Procedure/ (120876)
33 Crossover Procedure/ (40108)
34 Placebo/ (236677)
35 Randomi?ed controlled trial$.tw. (101620)
36 Rct.tw. (13868)
37 random allocation.tw. (1346)
38 randomly allocated.tw. (20579)
39 allocated randomly.tw. (1963)
40 (allocated adj2 random).tw. (745)
41 Single blind$.tw. (14514)
42 Double blind$.tw. (145091)
43 ((treble or triple) adj blind$).tw. (362)
44 placebo$.tw. (203019)
45 prospective study/ (266200)
46 or/28-45 (1422423)
47 case study/ (24405)
48 case report.tw. (263308)
49 abstract report/ or letter/ (907127)
50 or/47-49 (1189158)
51 46 not 50 (1384398)
52 27 and 51 (3959)
53 (2013$ or 2014$).em. (1884971)
54 (2013$ or 2014$).dp. (212803)
55 53 or 54 (1885690)
56 52 and 55 (410)
Database: EBM Reviews-Cochrane Central Register of Controlled Trials <January 2014>

Search strategy:
1 exp "Physical Education and Training"/ (1277)
2 (physical$ or training or exercise$).tw. (61997)
3 exp physical fitness/ (1836)
4 exp exercise/ (11692)
5 (yoga or tai chi or tai ji or walking or running or jogging or swimming or cycling or bicycling).tw. (9870)
6 exp yoga/ (214)
7 exp tai ji/ (133)
8 exp walking/ (2124)
9 exp running/ (1112)
10 exp jogging/ (36)
11 exp swimming/ (304)
12 exp bicycling/ (896)
13 aerobic.tw. (4058)
14 fitness.tw. (2416)
15 or/1-14 (68074)
16 (flush$ or flash$ or sweat$ or vasomotor).tw. (4227)
17 exp hot flashes/ (457)
18 exp flushing/ (139)
19 exp climacteric/ (5514)
20 (menopaus$ or perimenopaus$ or postmenopaus$).tw. (10946)
21 exp menopause/ or exp menopause, premature/ or exp perimenopause/ or exp postmenopause/ (5295)
22 climacter$.tw. (630)
23 or/16-22 (15173)
24 15 and 23 (1499)
25 limit 24 to yr="2013 -Current" (70)
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search strategy:
1 exp "Physical Education and Training"/ (13245)
2 (physical$ or training or exercise$).tw. (779516)
3 exp physical fitness/ (21299)
4 exp exercise/ (114797)
5 (yoga or tai chi or tai ji or walking or running or jogging or swimming or cycling or bicycling).tw. (131512)
6 exp yoga/ (1442)
7 exp tai ji/ (563)
8 exp walking/ (18971)
9 exp running/ (13258)
10 exp jogging/ (694)
11 exp swimming/ (18217)
12 exp bicycling/ (7443)
13 aerobic.tw. (53530)
14 fitness.tw. (38743)
15 or/1-14 (973082)
16 (flush$ or flash$ or sweat$ or vasomotor).tw. (61572)
17 exp hot flashes/ (2230)
18 exp flushing/ (1051)
19 exp climacteric/ (48213)
20 (menopaus$ or perimenopaus$ or postmenopaus$).tw. (66942)
21 exp menopause/ or exp menopause, premature/ or exp perimenopause/ or exp postmenopause/ (44796)
22 climacter$.tw. (3954)
23 or/16-22 (140049)
24 randomized controlled trial.pt. (363966)

25 controlled clinical trial.pt. (87650)
26 randomized.ab. (284281)
27 placebo.tw. (154362)
28 clinical trials as topic.sh. (167902)
29 randomly.ab. (206672)
30 trial.ti. (121423)
31 (crossover or cross-over or cross over).tw. (59389)
32 or/24-31 (900158)
33 exp animals/ not humans.sh. (3885146)
34 32 not 33 (829112)
35 15 and 23 and 34 (1878)
36 (2013$ or 2014$).ed. (1077600)
37 (2013$ or 2014$).dp. (1113935)
38 36 or 37 (1535052)
39 35 and 38 (208)

WHAT'S NEW

Last assessed as up-to-date: 3 March 2014.

Date	Event	Description
3 March 2014	New search has been performed	Review updated
3 March 2014	New citation required but conclusions have not changed	2 new studies were added to the review (Luoto 2012; Sternfeld 2014), and 3 previously included studies were deemed to be ineligible and have been excluded (Bergström 2005; Chatta 2008; Moriyama 2008), but this did not lead to a change in conclusions

HISTORY

Protocol first published: Issue 3, 2006

Review first published: Issue 4, 2007

Date	Event	Description
8 August 2011	New citation required and conclusions have changed	Date field ('Assessed as Up-to-date') was corrected
6 April 2011	New citation required and conclusions have changed	Conclusions have changed since the review was published in Issue 4, 2007
25 January 2011	Amended	Contact details have been updated
16 March 2010	New search has been performed	Updated review includes 5 new studies

(*Continued*)

7 November 2008	Amended	Review has been converted to new review format in this update
15 August 2007	New citation required and conclusions have changed	Substantive amendments have been made

CONTRIBUTIONS OF AUTHORS

Amanda Daley: conceived of the review, co-ordinated the review, collected and managed data for the review, read the final draft and served as guarantor of the review.

Helen Stokes-Lampard: collected and managed data for the review and read and commented on the final draft.

Chrstine MacArthur: collected data for the review and read and commented on the final draft.

Adèle Thomas: collected data for the review and read and commented on the final draft

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- University of Birmingham, UK.

Host institution of authors

External sources

- National Institute for Health Research (NIHR), UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The secondary outcomes of quality of life, tolerability and general symptomatology have been deleted and are no longer included in this review.

INDEX TERMS

Medical Subject Headings (MeSH)

*Exercise; *Menopause; *Sweating; Complementary Therapies; Estrogen Replacement Therapy; Hot Flashes [*therapy]; Randomized Controlled Trials as Topic; Sweat Gland Diseases [*therapy]; Walking; Yoga

MeSH check words

Female; Humans; Middle Aged